correct typographical errors. The Sequence Listing sheets and computer readable form have been replaced to correct an inadvertent error in SEQ ID NO:3. The error was the omission of the fifth and final amino acid of SEQ ID NO:3; the corrected Sequence Listing is now consistent with page 4, lines 17-18. No new matter has been added as a result of these amendments.

The Rejection of Claims 1, 2, 21, 44, 45, and 46 under 35 U.S.C. § 102(b)

Claims 1, 2, 21, 44, 45, and 46 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Barnett et al. (CA 2094658). Applicant respectfully traverses this rejection.

Claim 1 is directed to a composition for internally labeling a cell, comprising (1) a ligand which specifically binds to a cell surface antigen and is internalized by the cell, (2) an oligopeptide which is covalently bound to the ligand, and (3) a label which is covalently bound to the oligopeptide. The oligopeptide comprises at least one positively-charged amino acid residue and at least one D-amino acid residue. Dependent claims 2, 21, 44, 45, and 46 specify features of the oligopeptide, the label, and the ligand.

For a claim to be anticipated, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. Karsten Mfg. Corp. v. Cleveland Golf Co., 58 USPQ2d 1286, 1291 (Fed.Cir. 2001). Barnett et al. disclose a biochemical agent coupled with a carrier peptide that facilitates intracellular delivery of the biochemical agent. To facilitate delivery, Barnett et al. employ "a peptide that is comprised principally of independently selected positively charged amino acids, at

least 50% of which are in the non-naturally occurring, D-form." Barnett et al. at page 3, lines 25-27.

Despite teaching a carrier peptide comprising at least one positively-charged amino acid residue and at least one D-amino acid residue, Barnett et al. do not teach a ligand that specifically binds to a cell surface antigen. Instead, Barnett et al. use the carrier peptide as a "means for facilitating the uptake of biochemical agents targeted for intracellular delivery" (page 1, lines 28-29). The carrier peptide of Barnett et al. has properties which are inconsistent with it serving as the ligand of the subject claims. Barnett et al. merely teach that their carrier peptides "are particularly amenable to cellular uptake, and are capable additionally of localizing in the cell nucleus." Barnett et al. at page 2, lines 6-7. Barnett et al. do not teach specific binding, or any properties relevant thereto, of the composition to a cell surface antigen. Barnett et al. do not teach any kind of specific targetting to any particular type of cell. The Barnett invention merely "relates to chemical conjugates in which a carrier peptide amenable to cell uptake is coupled chemically with a biochemical agent selected for intracellular delivery." Barnett et al. at page 3, lines 21-22. Since Barnett et al. do not teach at least one element of Applicant's claim 1, *i.e.*, a ligand that specifically binds to a cell surface antigen, Barnett et al. do not anticipate this claim. Similarly, Barnett et al. do not anticipate claims 2, 21, 44, 45, and 46, which depend from claim 1 and include further elements. For these reasons, withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1-5 and 8-20 under 35 U.S.C. § 103(a)

Claims 1-5 and 8-20 are rejected as obvious over Barnett et al. (CA 209465) in view of Reist et al. (Cancer Research, 1996, Vol. 56, pp. 4970-4977) and Zalutsky et al. (US 5,302,700). The rejection is respectfully traversed.

Claim 1 is directed to a composition for internally labeling a cell, comprising (1) a ligand which specifically binds to a cell surface antigen and is internalized by the cell, (2) an oligopeptide which is covalently bound to the ligand, and (3) a label which is covalently bound to the oligopeptide. The oligopeptide comprises at least one positively-charged amino acid residue and at least one D-amino acid residue. Dependent claims 2-5 and 8-20 specify features of the oligopeptide, the label, and the ligand.

Barnett et al. is cited as teaching a composition for internally labeling a cell comprising multiple D-arginine residues. Reist et al. is cited as teaching a composition comprising ^{131}I or ^{125}I in a 5-iodo-3-pyridine carboxylate-labeled monoclonal antibody against EGFRvIII. Reist et al. is cited as further teaching the benefits of carrying a positively charged moiety for resisting lysosomal degradation and enhancing cellular retention of the radiolabel. Zalutsky et al. is cited as teaching the radioiodination of peptides via tyrosine or lysine.

The Office Action states that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a ligand comprising the monoclonal antibody that specifically binds EGFRvIII, attached to the carrier peptide described by Barnett. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Reist et

al. on the specific binding and internalization of the radiolabeled anti-EGFRvIII antibody in glioma, lung, breast, and ovarian carcinomas." Office Action at Page 4, lines 12-18.

The Supreme Court has ruled that secondary considerations such as unexpected results, important advantages, synergism, and others are relevant as indicia of obviousness or nonobviousness. *Graham v. John Deere* Co., 383 U.S. 1, 17-18 (1966). Moreover, evidence of secondary consdierations, where present, must be considered in a determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corporation,* 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). Importantly, Applicant has discovered that an oligopeptide comprising both one or more D-amino acids and one or more positively charged amino acids unexpectedly improves retention of label by the cell, compared with either one or more D-amino acids or one or more positively charged groups alone. The degree of improvement is much greater than that observed by Reist et al. using the positively charged 5-iodo-3-pyridinecarboxylate moiety. This can be seen by comparing the cellular retention of the radiolabel in Reist et al. with that obtained using a positively charged oligopeptide of the invention. While Reist et al. disclose an increase in intracellular retention of up to 65% over the iodinated antibody (see page 4970, column 1, lines 13-15), Fig. 3 of Applicant's specification demonstrates that a composition using α-N-Ac-D-Lys-D-Arg-D-Tyr-D-Arg-D-Arg provided a three- to four-fold (300-400%) increase in label retention after 24 hours compared to the radioiodinated antibody lacking the oligopeptide. Govindan et al. (J Nuclear Med 39:989 (1998)), cited in a previous office action, reported only a two- to three-fold increase in retention using D-amino acids without positive charge. None of the cited references suggests or even hints at the benefit of using an oligopeptide comprising both one or more D-amino acids and one or more

positively charged amino acids. These unexpected results, therefore, rebut any *prima facie* presumption of obviousness over Barnett et al. in view of Reist et al. and Zalutsky et al.

Furthermore, obviousness can only be established by combining teachings where there is some motivation to do so. *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Barnett et al. teach the use of carrier peptides to facilitate the uptake of biochemical agents which otherwise are poorly taken up by target cells. In contrast, Reist et al. and Zalutsky et al. teach radiolabeling compounds such as antibodies that are already capable of being internalized by the cell and thus do not require facilitation of their uptake. Furthermore, Reist et al. relates to compositions that improve the retention, not the uptake, of labels within target cells.

Based on these teachings, there would have been no motivation to use the carrier protein of Barnett et al. to facilitate the uptake of compounds taught by Reist et al. and Zalutsky et al. The compounds of Reist et al. and Zalutsky et al. are unlike the "biochemical agents" taught in Barnett et al. in that they are readily internalizable through binding with a cell surface receptor. Therefore, these compounds do not require facilitation for cellular uptake. From the teachings of the references, there would have been no expectation that the carrier peptide of Barnett et al. would facilitate the uptake or retention of the compounds disclosed in Reist et al. and Zalutsky et al. and thus no motivation for making the proposed combination.

Likewise, there would have been no motivation to use the carrier protein of Barnett et al. to increase the cellular retention of a labeled composition, since none of the references suggest or even hint at such an effect of a carrier peptide. Therefore, there

would have been no motivation to combine the carrier peptide of Barnett et al. with the radiolabeled compositions of Reist et al. and Zalutsky et al. Since such a motivation is lacking, these references do not render Applicants' claims 1-5 and 8-20 obvious.

Moreover, the Office Action asserts that motivation to combine the cited references is provided by "the teachings of Reist et al. on the specific binding and internalization of the radiolabeled anti-EGFRvIII antibody in glioma, lung, breast, and ovarian carcinomas." Emphasis added. Reist et al. teach the specific targeting of label to tumor cells based on specific binding of a ligand to a cell surface antigen found in tumor cells. The carrier peptide of Barnett et al. however, promotes non-specific uptake of a biochemical agent across cell membranes. "Such carrier peptides can be utilized to facilitate cellular uptake and nuclear delivery of various biochemical agents. . . ." Barnett et al. at page 2, lines 16-17. Thus, Reist et al. teach away from the non-specific uptake of Barnett et al., which would introduce an agent or label into tumor cells and normal cells with equal efficacy, thereby destroying the tumor specificity taught by Reist et al. Further, adding the carrier peptide of Barnett et al., which generally promotes cellular uptake, to the composition of Reist et al., which requires the selective uptake into certain cells (*e.g.*, tumor cells) but not other cells, would render the Reist et al. composition unsuitable for its intended purpose because the resulting composition would lack cell specificity. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or movtivation to make the proposed modification." MPEP 2143.01, citing *In re Gordon,* 733 F.2d 900 (Fed. Cir. 1984).

Therefore, for the reasons discussed above, the withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1-20 under 35 U.S.C. § 103(a)

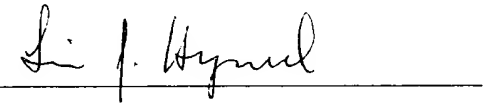
Claims 1-20 are rejected as obvious over Barnett et al. (CA 209465) and Reist et al. (Cancer Research, 1996, Vol. 56, pp. 4970-4977) and Zalutsky et al. (US 5,302,700) in further view of Emery et al. (Antibody Engineering, 1995, p. 159-181). While claims 1-20 are nominally rejected, the Office Action only discusses claims 6 and 7 which deal with interspecies and humanized antibodies. Applicant respectfully traverses this rejection.

The teachings for which Barnett et al., Reist et al., and Zalutsky et al. are cited are stated above. Emery et al. is cited as teaching that the use of humanized or murine variable regions grafted onto human framework regions increases the half-life of the antibodies, imparts greater effector functions by means of the human framework constant regions, and avoids human anti-mouse hypersensitivity reactions. The Office Action states that is would have been *prima facie* obvious to one of ordinary skill in the art to make a ligand comprising a humanized or interspecies monoclonal antibody that specifically binds to EGFRvIII which is covalently attached to the carrier peptide as taught by Barnett et al. For reasons stated previously, however, secondary considerations relating to the unexpected effect of combining an oligopeptide comprising both D-amino acids and positively-charged residues with a ligand and a label rebut any presumption of *prima facie* obviousness of making this combination. Also, there is no motivation to use the carrier peptide of Barnett et al., which is taught to non-specifically facilitate cellular

uptake, to stabilize the compounds of Reist et al. or Zalutsky et al. Emery et al. do not suggest the unexpected benefit of Applicant's claimed composition. Nor do Emery et al. provide a motivation for the proposed combination of references.

Accordingly, in view of the above amendments and remarks, all pending claims of this application are believed to be in condition for allowance, and such action is respectfully requested. This response is believed to completely address all of the issues raised Examiner's Office Action dated October 22, 2001.

Respectfully submitted,

By 

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VERSION OF REPLACEMENT PARAGRAPH WITH MARKINGS TO SHOW CHANGES

In the specification, beginning at page 28, line 25:

A paired-label *in vitro* assay was performed to compare the internalization and cellular processing of mAb L8A4 labeled with ^{131}I using Iodogen and ^{125}I using the oligopeptide linker method of this invention. Monoclonal antibody L8A4 was labeled using the oligopeptide linker as follows. The peptide α-N-Ac-D-Lys-D-Arg-D-Tyr-D-Arg-D-Arg (KRYRR) (SEQ ID NO:3) was obtained from a custom synthesis laboratory and labeled with ^{125}I using the Iodogen method. Reverse-phase HPLC was used to isolate[d] ^{125}I-labeled KRYRR (SEQ ID NO:3) in >97% yield, and the labeled peptide was activated by reaction[s] with sulfo-SMCC at room temperature for 30 min. Murine anti-EGFRvIII mAb L8A4 was reacted with 2-imino thiolane to generate free thiol groups[,] and then reacted with activated ^{125}I-labeled peptide-L8A4. The conjugate was isolated over a Sephadex G-25-PD10 column. The yield [is] was about 35%.